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European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3162

REVIEW ARTICLE

Medical therapy of cardiogenic shock: Contemporary use of inotropes and vasopressors

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Received 5 October 2023; revised 23 January 2024; accepted 28 January 2024

Cardiogenic shock is a primary cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion and can lead to multi-organ failure and death depending on its severity. Inadequate cardiac contractility or cardiac power secondary to acute myocardial infarction remains the most frequent cause of cardiogenic shock, although its contribution has declined over the past two decades, compared with other causes. Despite some advances in cardiogenic shock management, this clinical syndrome is still burdened by an extremely high mortality. Its management is based on immediate stabilization of haemodynamic parameters so that further treatment, including mechanical circulatory support and transfer to specialized tertiary care centres, can be accomplished. With these aims, medical therapy, consisting mainly of inotropic drugs and vasopressors, still has a major role. The purpose of this article is to review current evidence on the use of these medications in patients with cardiogenic shock and discuss specific clinical settings with indications to their use.

Keywords Cardiogenic shock • Inotropes • Vasopressors • Mechanical circulatory support

Introduction

Cardiogenic shock (CS) is a clinical syndrome characterized by a primary cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion due to an inadequate cardiac output (CO), that may result in multi-organ failure and death.[1,2] The presence of clinical signs of hypoperfusion (i.e. cold clammy extremities, oliguria, mental confusion, dizziness and narrow pulse pressure) and/or biochemical manifestations of hypoperfusion (i.e. elevated serum creatinine, metabolic acidosis and elevated serum lactate) is crucial for the diagnosis, while hypotension (systolic blood pressure [BP] <90 mmHg), that is often the primary clinical manifestation of CS,[3] is not a key feature *per se*, as BP can be preserved by compensatory vasoconstriction (with or without vasopressor agents), albeit at the cost of further impaired tissue perfusion and oxygenation.[1,4,5] The Society for Cardiovascular Angiography and Interventions (SCAI) classification[6] describes five evolutive stages of CS (*Table 1*), ranging from patients at risk of CS (stage A), to pre-shock characterized by acute hypotension but preserved organ perfusion (stage B), to overt shock (stages C, D, and E). Of note, SCAI staging is a dynamic process and its evaluation 24 h after shock onset is better suited to predict mortality, compared with the initial assessment.[7]

The prevalence of CS varies according to its definition and clinical setting, but accounts for about 2–5% of acute heart failure (HF) presentations.[1] Ventricular failure subsequent to acute

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Table 1 SCAI classification for cardiogenic shock[6]

A	**At risk of CS** (patient who is not currently experiencing signs or symptoms of CS)	Normal JVP Lung sound Warm and well perfused	Normal exams	Normotensive (SBP ≥100 mmHg or normal for patient) Haemodynamics: CI ≥ 2.5 L/min CVP <10 mmHg PCWP ≤15 mmHg PA saturation ≥65%
B	**Beginning CS** (relative hypotension or tachycardia without hypoperfusion)	Elevated JVP Rales in lung fields Warm and well perfused	Normal lactate Minimal renal function impairment Elevated BNP	SBP <90 mmHg OR MAP <60 mmHg OR >30 mmHg SBP drop from baseline Heart rate ≥100 bpm Haemodynamics: CI ≥2.2 L/min PA saturation ≥65%
C	**Classic CS** (hypoperfusion that requires intervention beyond volume resuscitation)	May include any of: Looks unwell Panicked Ashen, mottled, dusky Volume overload Extensive rales Killip class 3 or 4 BiPAP or mechanical ventilation Cold, clammy Acute alteration in mental status Urine output <30 ml/h	May include any of: Lactate ≥2 mmol/L Creatinine doubling OR > 50% drop in GFR Increased LFTs Elevated BNP	May include any of: >30 mmHg SBP drop from baseline AND drugs/device used to maintain BP above target CI <2.2 L/min PCWP >15 mmHg RAP/PCWP ≥0.8 PAPi <1.85 CPO ≤0.6 W
D	**Deteriorating/doom CS** (similar to category C but getting worse)	Any of stage C	Any of stage C AND: Deteriorating	Any of stage C AND: Requiring multiple pressors OR addition of MCS devices to maintain perfusion
E	**Extremis CS** (cardiac arrest with ongoing CPR and/or ECMO, being supported by multiple interventions)	Near pulselessness Cardiac collapse Mechanical ventilation Defibrillator used	'Trying to die' CPR (A-modifier) pH ≤7.2 Lactate ≥5 mmol/L	No SBP without resuscitation PEA or refractory VT/VF Hypotension despite maximal support

BiPAP, bilevel positive airway pressure; BNP, brain natriuretic peptide; BP, blood pressure; CI, cardiac index; CPO, cardiac power output; CPR, cardiopulmonary resuscitation; CS, cardiogenic shock; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; JVP, jugular venous pressure; LFT, liver function test; MAP, mean arterial pressure; MCS, mechanical circulatory support; PA, pulmonary artery; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PEA, pulseless electrical activity; RAP, right atrial pressure; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachyarrhythmia.

myocardial infarction (AMI) remains the most frequent cause of CS (AMI-CS), although its contribution has declined over the past two decades, in parallel with an increase of CS of other aetiologies.[8–10] Despite some advances in CS management, it is still burdened by an extremely poor prognosis, with in-hospital mortality ranging from 30% to 60%.[11–13] Management of CS is based on (i) immediate stabilization and transfer to an intensive care setting, (ii) recognition and treatment of the underlying cause, and (iii) correction of end-organ hypoperfusion to prevent or reverse organ failure, which is independently associated with in-hospital mortality and greater resource utilization.[1,14,15]

Coronary reperfusion is the main evidence-based therapeutic intervention for patients with AMI-CS,[8,16] preferring culprit vessel percutaneous coronary intervention in case of multivessel disease.[17] An important goal in CS, either AMI-CS and non-AMI-CS, is to address reduced myocardial function as well as hypotension, using inotropic and/or vasopressor agents.[2] Despite a persistent class IIb indication according to current guidelines, these drugs are administered in approximately 90% of patients with CS in clinical practice,[1] especially in non-ischaemic aetiology.[18] However, the use of these drugs has been associated with increased mortality, possibly due to an increased incidence of arrhythmias and increased myocardial oxygen consumption.[19–24] It is therefore recommended that they are administered at the lowest possible dose and the shortest possible duration.[1]

Although transfer to specialized tertiary care centres and escalation to mechanical circulatory support (MCS) is advocated in case of CS refractory to medical treatment[1,25], the use of inotropes and/or vasopressors remains mandatory for the initial stabilization of the patient.[2] Therefore, we aimed to review current evidence and approaches on medical therapy in CS, mainly focusing on the use of inotropic and vasopressor agents.

Overview of inotropic therapies

The term 'inotrope' derives from the Ancient Greek terms *ís* (sinew, force, power) and *trópos* (i.e. –tropic, affecting or changing), and is intimately connected with pharmaceuticals clinically used for the treatment of low CO conditions such as CS.[26]

Catecholamines and phosphodiesterase-III (PDE-III) inhibitors all increase myocardial contractility through an increase in intracellular Ca^{2+} concentrations.[26–29] For this reason, these agents were classified as cardiac calcitropes.[26] Catecholamines such as dobutamine, dopamine, epinephrine and norepinephrine increase

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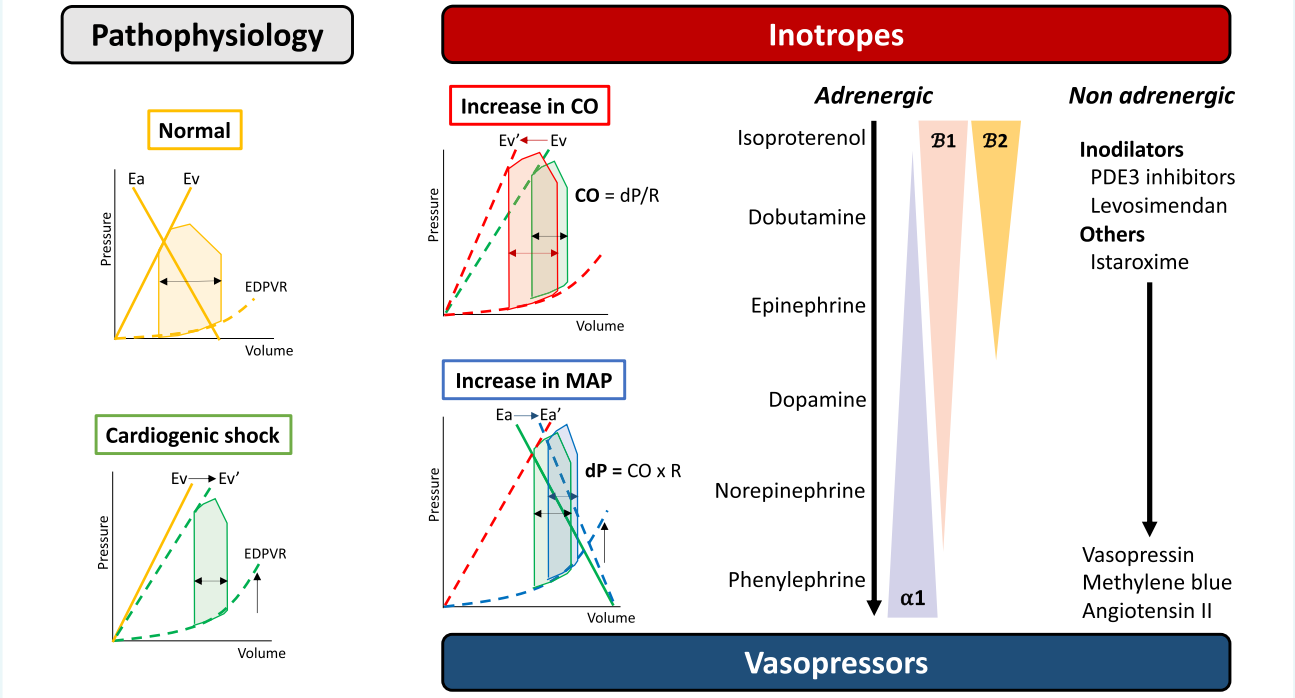

Figure 1 Pharmacodynamic effects of vasopressors/inotropes. The balance between α- and β-adrenergic receptor stimulation determines the main effects of catecholamines. Pressure–volume loops illustrate the haemodynamics of cardiogenic shock amongst patients with previously normal heart function, resulting in increased ventricular volumes and filling pressures and reduced contractility and stroke volume (right-shift). Drugs that act mainly by increasing mean arterial pressure (MAP) (vasopressors), increasing left ventricular afterload (Ea′), result in a further shift of the curve to the right (blue line). Instead, drugs with pure inotropic properties (increasing Ev′) are able to shift the curve to the left with increased contractility and stroke volume (red line). CO, cardiac output; PDE3, phosphodiesterase-III; Ea, elastance of arterial system; EDPVR, end-diastolic pressure–volume relationship; Ev, ventricular elastance; P, pressure; R, resistance.

contractility binding membrane-bound G-protein coupled adrenergic receptors. The activation of these receptors stimulates the formation of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase and, subsequently, the activation of protein kinase A (PKA). PKA phosphorylases several downstream targets, including phospholamban (that increases the sarcoplasmic reticulum Ca^{2+} absorption by sarcoplasmic reticulum Ca^{2+} ATPase isoform 2a [SERCA2a]), ryanodine receptors (which then release more Ca^{2+} during depolarization) and troponin C (that facilitates exposure to actin for myosin).[26,30] PDE-III inhibitors (e.g. milrinone and enoximone) act on the same pathway as catecholamines blocking the degradation of cAMP.[30] Levosimendan has a peculiar mechanism of action as it acts on troponin C favouring actin–myosin cross-bridging and myocardial contraction, opens ATP-dependent K^+ channels in myocytes and vascular smooth muscle cells with peripheral vasodilatation, and is a PDE-III inhibitor.[31] Istaroxime is a novel inotropic drug acting not only as a non-glycoside Na^+/K^+ ATPase inhibitor but also, and likely to greater extent, improving SERCA2a activity with increased intra-sarcoplasmic reticulum calcium uptake during diastole and an increased calcium release at the subsequent contraction.[32] Differently from the previous agents, it is still experimental and not available for current therapy. Although catecholamines and PDE-III inhibitors have a role in CS management, their long-term use is associated with increased adverse effects and mortality, and this is likely due to the increase in intracellular calcium concentrations.[19–24] Research has therefore shifted to agents acting directly on the sarcomere. Such drugs are termed cardiac myotropes.[26] As mentioned above, levosimendan also acts as a Ca^{2+} sensitizer on the troponin–tropomyosin complex, so it can also be considered a cardiac myotrope.[33]

Cardiac mitotropes have also been proposed, e.g. innovative drugs targeting the mitochondrial production of energy that is available to the myocardium.[26] Currently, limited data are available on the safety and efficacy of these drugs, almost all coming from small non-randomized trials, and without data available in the context of CS.[26]

Regarding catecholamines (the most commonly used drugs in CS), the balance between α- and β-adrenergic receptor stimulation determines their main effects, ranging from pure inotropes (i.e. drugs increasing CO) to pure vasopressors (i.e. drugs increasing mean arterial pressure (MAP) (*Figure 1*). However, the arbitrary vasopressor and inotrope definitions for catecholamines, in particular when the term 'vasopressor' is used to describe predominantly peripheral arterial vasoconstrictive properties, do not necessarily reflect the true *in vivo* effects of these agents.

Table 2 shows the main scientific evidence from randomized trials on the use of inotropic/vasopressor drugs in CS.[22,34–46]

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Table 2 Randomized controlled trials on the use of inotropes/vasopressors in cardiogenic shock

Trial, year	Drugs	No. of patients	Main inclusion criteria	Primary endpoint	Results	Safety
SOAP-II, 2010[34]	Dopamine vs. norepinephrine	1679 (dopamine $n=858$; norepinephrine $n=821$); among these patients, 280 had CS (135 in the dopamine group and 145 in the norepinephrine group)	Shock (defined as MAP <70 mmHg or SBP <100 mmHg with signs of hypoperfusion) with need for vasopressor agent	Death at 28 days	Increased rate of death among the 280 patients with CS treated with dopamine ($p=0.03$)	More arrhythmic events in the dopamine group (24.1%) vs. norepinephrine group (12.4%) ($p<0.001$)
CAT, 2008[35]	Epinephrine vs. norepinephrine	280 ($n=140$ in each treatment arm); among these, 128 had CS (64 in each treatment arm)	Need for infusion of epinephrine or norepinephrine for any cause	Time taken to achieve a MAP ≥70 mmHg for >24 h without vasopressors	No difference in the time to achieve MAP both in the whole population and in CS setting (RR 0.89, 95% CI 0.62–1.27, $p=0.49$)	Development of significant tachycardia and lactic acidosis with epinephrine, in addition to increased insulin requirements
OptimaCC, 2018[36]	Epinephrine vs. norepinephrine	57 (epinephrine $n=27$; norepinephrine $n=30$)	AMI-CS successfully revascularized, SBP <90 mmHg or MAP <65 mmHg, cardiac index <2.2 L/min/m^2, PCWP >15 mmHg, LVEF <40% and evidence of tissue hypoperfusion	Change in cardiac index (primary efficacy endpoint); occurrence of refractory CS (primary safety endpoint)	Cardiac index evolution was similar between groups ($p=0.43$). Higher incidence of refractory shock in the epinephrine group (37% vs. 7%, $p=0.008$)	HR increased significantly with epinephrine ($p<0.0001$); increase in cardiac double product ($p=0.0002$) and lactic acidosis ($p<0.0001$) with epinephrine
Levy *et al.*, 2011[37]	Norepinephrine-dobutamine vs. epinephrine	30 ($n=15$ in each treatment arm)	Non-AMI-CS (defined as LVEF <30% and cardiac index <2.2 L/min/m^2, absence of hypovolaemia, lactate >2 mmol/L, MAP <60 mmHg or SBP <90 mmHg, urine output <0.5 ml/kg/h, signs of hypoperfusion, no signs of acute cardiac ischaemia)	Haemodynamic effects using the drugs to obtain a MAP of 65–70 mmHg	Both regimes increased cardiac index and oxygen-derived parameters in a similar manner	HR, lactate levels and PCO_2 gap, a surrogate for splanchnic perfusion adequacy, increased in the epinephrine group ($p<0.05$, $p<0.01$ and $p<0.01$, respectively)
DOREMI, 2021[38]	Dobutamine vs. milrinone	192 ($n=96$ in each treatment arm)	CS SCAI B-D	Composite of in-hospital death from any cause, resuscitated cardiac arrest, cardiac transplant or MCS, non-fatal MI, TIA/stroke or RRT	Primary endpoint was 49% in the milrinone group vs. 54% in the dobutamine group (RR 0.90, 95% CI 0.69–1.19, $p=0.47$)	No significant differences in HR, MAP, serum lactate level, serum creatinine level, or hourly urine output between the treatment groups
Fuhrmann *et al.*, 2008[39]	Enoximone vs. levosimendan	32 ($n=16$ in each group)	Refractory CS patients requiring additional therapy	Survival at 30 days	Survival rate at 30 days was higher in the levosimendan group (69% vs. 37%, $p=0.023$)	N/A
LIDO, 2002[40]	Dobutamine vs. levosimendan	203 (levosimendan $n=103$; dobutamine $n=100$)	Low-output HF (including ADHF)	Proportion of patients with haemodynamic improvement at the end of the 24-h infusion period	Primary endpoint met in 28% of patients in the levosimendan group vs. 15% in the dobutamine group (hazard ratio 1.9, 95% CI 1.1–3.3, $p=0.022$)	Angina pectoris, chest pain, or myocardial ischaemia more frequent in the dobutamine group, in addition to a higher proportion of patients with rate and rhythm disorders; trend towards a higher frequency of headache or migraine in the levosimendan group
SURVIVE, 2007[22]	Dobutamine vs. levosimendan	1327 (levosimendan $n=664$; dobutamine $n=663$)	ADHF ± low cardiac output	All-cause mortality at 180 days	No significant difference in 180-day death (26% in the levosimendan group vs. 28% in the dobutamine group; hazard ratio 0.91, 95% CI 0.74–1.13, $p=0.40$)	Higher incidence of cardiac failure in the dobutamine group; higher incidence of AF, hypokalaemia and headache in the levosimendan group
Samimi-Fard *et al.*, 2008[41]	Dobutamine vs. levosimendan	22 ($n=11$ in each group)	AMI-CS	Cardiac death at 12 months	No significant difference in 1-year cardiac death ($p=0.24$)	N/A
LEAF, 2013[42]	Levosimendan vs. placebo	61 (levosimendan $n=30$; placebo $n=31$); among these, 9 had CS (levosimendan $n=4$; placebo $n=5$)	STEMI with signs of decreased wall motion in at least 3 of 16 segments of the LV + clinical HF	Wall motion score index at 5 days	Larger improvement from baseline to day 5 in the levosimendan group (from 1.94 ± 0.20 to 1.66 ± 0.31 vs. 1.99 ± 0.22 to 1.83 ± 0.26, $p=0.031$)	Significantly more episodes of hypotension during study drug infusion in the levosimendan group (67% vs. 36%, $p=0.029$); in CS subgroup, NSVT was observed in 3 patients in the placebo group and in 1 in the levosimendan group

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Table 2 (Continued)

Trial, year	Drugs	No. of patients	Main inclusion criteria	Primary endpoint	Results	Safety
García-González *et al.*, 2006[43]	Levosimendan vs. dobutamine	22 ($n = 11$ in each group)	AMI-CS	Increase >30% in CPO, after 24 h of therapy	Levosimendan had a consistently better effect on CPO than dobutamine ($p < 0.05$)	Both levosimendan and dobutamine increased HR (6.7 bpm vs. 5.8 bpm, $p = 0.49$); no further change in SBP and no serious side effects in either group
SEISMIC, 2022[44]	Istaroxime vs. placebo	60 (istaroxime $n = 29$; placebo $n = 31$)	AHF-related pre-CS (SCAI B) with LVEF ≤40%	Change in SBP from baseline to 6 h	SBP change was 53.1 mmHg × hour with istaroxime vs. 30.9 mmHg × hour with placebo ($p = 0.017$)	Treatment emergent adverse events in 93% in the istaroxime group vs. 81% in the placebo group
SHOCK-2, 2007[45]	L-N-monomethyl-arginine vs. placebo	79 (arginine $n = 59$; placebo $n = 20$)	AMI-CS	Absolute change in MAP	Modest increases in MAP at 15 min vs. placebo without differences at 2 h	L-N-monomethyl-arginine well tolerated, safety profile similar to placebo
TRIUMPH, 2007[46]	Tilarginine vs. placebo	398 (tilarginine $n = 206$; placebo $n = 198$; assignment unknown $n = 2$)	AMI-CS	All-cause mortality at 30 days	No differences in 30-day all-cause mortality (48% vs. 42%; hazard ratio 1.14, 95% CI 0.92–1.41, $p = 0.24$)	No significant differences in safety

ADHF, acute decompensated heart failure; AF, atrial fibrillation; AHF, acute heart failure; AMI, acute myocardial infarction; CI, confidence interval; CPO, cardiac power output; CS, cardiogenic shock; HF, heart failure; HR, heart rate; LV, left ventricle; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MCS, mechanical circulatory support; MI, myocardial infarction; N/A, not available; NSVT, non-sustained ventricular tachycardia; PCO_2, partial pressure of carbon dioxide; PCWP, pulmonary capillary wedge pressure; RR, relative risk; RRT, renal replacement therapy; SBP, systolic blood pressure; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

Dopamine

Dopamine is an endogenous central neurotransmitter, immediate precursor of norepinephrine in the biosynthesis process.[47] It has been used intravenously to treat CS since the 1970s.[48] At low doses (<3 μg/kg/min), stimulation of dopaminergic D_1 post-synaptic receptors concentrated in the coronary, renal, mesenteric, and cerebral beds and D_2 pre-synaptic receptors present in the vasculature and renal tissues promotes vasodilatation and increased blood flow to these tissues.[47] However, the benefits of 'renal doses' of dopamine have remained controversial.[49–52] Intermediate doses of dopamine (3–10 μg/kg/min) activate β-adrenergic receptors promoting norepinephrine release and inhibiting reuptake in pre-synaptic sympathetic nerve terminals, which result in increased cardiac contractility and chronotropy, with a mild increase in systemic vascular resistance (SVR). At higher infusion rates (10–20 μg/kg/min), dopamine acts primarily as an α-adrenergic agonist resulting in peripheral vasoconstriction.[47,48]

Several side effects may manifest with the use of dopamine, especially with increasing dosage, including the induction of tachyarrhythmias[34] and a progressive reduction in splanchnic and renal perfusion, to more rare complications such as inhibition of the release of hormones from the anterior pituitary gland, disturbances in the activity of T cells and alteration in chemoreflex sensitivity and respiratory activity.[53]

There is limited evidence of the efficacy of dopamine from randomized controlled trials. In the SOAP-II (Sepsis Occurrence in Acutely Ill Patients II) randomized trial,[34] patients with shock ($n = 1679$) were assigned to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain BP. Globally, there was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group, $p = 0.10$). However, a subgroup analysis showed that dopamine was associated with an increased rate of death at 28 days among the 280 patients with CS ($p = 0.03$), although the p-value for interaction between aetiology and treatment strategy was not significant ($p = 0.87$). Moreover, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (24.1% vs. 12.4%, $p < 0.001$). In a meta-analysis,[54] norepinephrine was associated with lower 28-day mortality as compared to dopamine among patients with CS. Lastly, in a propensity-score matching analysis from the European Society of Cardiology (ESC)-HF Long-Term Registry, dopamine was associated with worse short- and long-term outcomes compared with other inotropes and vasopressors.[20]

Norepinephrine

Norepinephrine is an endogenous catecholamine normally synthesized, stored, and released from sympathetic neurons.[48] Norepinephrine has strong α_1-adrenergic and moderate β_1-adrenergic effects that make it a vasoconstrictor but a less potent inotrope. Since norepinephrine is virtually a 'pure' vasoconstrictor, it may reduce CO in patients with cardiac dysfunction because of afterload increase (*Figure 1*).[53,55] In addition, it has chronotropic properties.[48] Typically, norepinephrine is infused at

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0.02–1 μg/kg/min, with tapering started with a rate of 0.1 μg/kg/min per hour. As with all catecholamine-based therapies, it can be associated with tachycardia, myocardial ischaemia, and arrhythmia.[48] However, thanks to its plasma half-life of 5–10 min, because of its rapid metabolism in the liver and tissues, norepinephrine is readily controllable in a concentration-dependent manner.[53]

As previously described, the multicenter SOAP-II trial[34] showed a trend toward lower 28- day mortality under norepinephrine in addition to a lower arrhythmic risk. Regarding the comparison with epinephrine, in the OptimaCC trial[36] that randomized 57 patients with AMI-CS to these two agents, both drugs increased MAP, but epinephrine-treated patients showed higher rates of lactic acidosis, marked and sustained increases in heart rate (HR), and increased cardiac double product, a marker of myocardial oxygen consumption. Most importantly, patients in the epinephrine group had an increased occurrence of refractory shock, with no significant difference in mortality between the two groups (60-day mortality of 52% in the epinephrine group and 37% in the norepinephrine group, $p = 0.25$). Negative results were also found in an individual data meta-analysis including 2583 patients. Across all cohorts included ($n = 16$), risk of short-term death was significantly higher in epinephrine-treated patients (odds ratio [OR] 3.3, 95% confidence interval [CI] 2.8–3.9) compared to patients treated with other drug regimens for CS. After adjusting for age, gender, ischaemic heart disease, estimated glomerular filtration rate and left ventricular (LV) ejection fraction at admission, mortality remained striking in epinephrine-treated patients (adjusted OR 4.7, 95% CI 3.4–6.4).[56] Consequently, the ESC guidelines and the American Heart Association/American College of Cardiology guidelines recommend norepinephrine as the vasopressor of choice in CS and marked hypotension.[2,57] In a recent retrospective cohort study, CS patients treated with norepinephrine, alone or in combination with other vasoactive medication, had an increase in short-term mortality compared with patients in the non-norepinephrine group (41% vs. 30%, $p = 0.017$), while no significant difference was found in long-term survival rates ($p = 0.477$ at 1 year).[58] Also in the ESC-HF Long-Term Registry, norepinephrine was associated with a trend towards increased long-term risk of death, although it did not reach statistical significance (hazard ratio 3.76, 95% CI 0.90–15.66).[20] The multinational CardShock study showed that the use of norepinephrine was associated with increased 90-day mortality.[59] Similarly, a post-hoc analysis of the ALARM-HF dataset showed that norepinephrine use was associated with more than a 2.5-fold increase of in-hospital mortality among patients with acute HF, although there was no further analysis of the CS subgroup.[60] However, these observational findings may be biased as patients receiving norepinephrine are commonly sicker, and more clinical studies are needed to further evaluate the efficacy and safety of norepinephrine as a first-line vasopressor in CS.

Epinephrine

Epinephrine is an endogenous catecholamine with affinity for β_1-, β_2- and α_1-receptors present in cardiac and vascular smooth muscle.[47] Therefore, epinephrine increases SVR via α_1-receptor-dependent vasoconstriction and increases CO via its binding to β_1-receptors. At low doses, the action on β-adrenergic receptors prevails, while with the increase of the dose the action on the α_1-receptors is enhanced.[47] Clinically, coronary blood flow is improved through increased relative diastolic duration and through stimulation of myocytes to release local vasodilators, which largely counterbalance direct α_1-mediated coronary vasoconstriction. In addition, arterial and venous pulmonary pressures are increased through direct pulmonary vasoconstriction and increased pulmonary blood flow.[47]

Epinephrine doses above 0.3–0.5 μg/kg/min are considered high, but there is no defined maximum epinephrine dose for refractory shock.[55] However, high and prolonged doses can cause direct cardiac toxicity through damage to arterial walls, which causes focal regions of myocardial contraction band necrosis, and through direct stimulation of myocyte apoptosis.[61] In addition, epinephrine promotes the development of atrial and ventricular arrhythmias and may cause elevated lactate levels that could not only be directly harmful but might also confound the serial trending of serum lactate levels.[55] In a single-centre study including 30 hypotensive patients with non-ischaemic CS, short-term (24 h) infusion of epinephrine or the combination of norepinephrine and dobutamine, titrated to achieve the same target BP, similarly increased cardiac index, oxygen delivery, and oxygen consumption.[37] However, epinephrine administration was associated with more arrhythmic events, a rise in lactate levels and less diuresis compared to norepinephrine-dobutamine.[37] In a randomized controlled trial including 280 patients with need for epinephrine or norepinephrine infusion for any cause, 128 had acute circulatory failure. There was no difference in the time to achieve MAP goals in this subgroup of patients (relative risk 0.89, 95% CI 0.62–1.27, $p = 0.49$) between epinephrine and norepinephrine. In addition, there was no difference in 28- and 90-day mortality. However, also in this case, epinephrine was associated with the development of significant but transient increase in lactate levels and tachycardia.[35] An important contribution to the clinical use of epinephrine in CS comes from the already mentioned OptimaCC trial, where epinephrine was associated with a higher incidence of refractory shock as compared to norepinephrine.[36] Epinephrine results in an increased likelihood of death even in observational studies.[56,59,62] Therefore, epinephrine is not recommended as a first-line agent for CS.[2] This drug still has a pivotal role in cardiac arrest, being associated with a significantly higher rate of 30-day survival versus placebo among patients with out-of-hospital cardiac arrest enrolled in the PARAMEDIC2 (Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest) trial, although severe neurologic impairment at hospital discharge was more frequent in the epinephrine group in such trial.[63]

Dobutamine

Unlike other catecholamines, dobutamine is of synthetic origin with a strong affinity for both β_1- and β_2-receptors, which it binds to at a 3:1 ratio.[53] With its cardiac β_1-stimulatory effects, dobutamine is a potent inotrope, with weaker chronotropic activity. Vascular smooth muscle binding results in combined α_1-adrenergic agonism and antagonism, as well as β_2-stimulation, such that the net

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vascular effect is often mild vasodilatation, particularly at lower doses (≤5 μg/kg/min). Doses up to 15 μg/kg/min increase cardiac contractility without greatly affecting peripheral resistance, likely owing to the counterbalancing effects of α_1-mediated vasoconstriction and β_2-mediated vasodilatation. However, vasoconstriction progressively dominates at higher infusion rates.[47] Tapering is started with a rate of 0.1 μg/kg/min per hour or 0.5 μg/kg/min at 6 h.

Clinically, dobutamine increases CO in patients with severe HF by increasing stroke volume and decreasing SVR.[64–66] From the beginning, it was suggested that dobutamine might have an advantage over dopamine, as it does not increase sympathetic norepinephrine signalling or peripheral vasoconstriction[67] by increasing or maintaining BP solely by increasing CO.[48] For this reason, dobutamine's effects on MAP can vary considerably because they depend on the relative changes in CO and SVR from baseline values. In CS, when baseline CO is low and SVR is high, dobutamine may raise MAP by increasing stroke volume and CO while SVR declines. However, if SVR drops excessively, the net effect of dobutamine infusion may be hypotension if CO has not increased proportionately.[55] In this case, concomitant use of norepinephrine may be considered.

Despite its mild chronotropic effects at low-to-medium doses, dobutamine significantly increases myocardial oxygen consumption. Malignant ventricular arrhythmias can be observed at any dose and dobutamine should be used with caution in patients with atrial fibrillation because it can increase atrio-ventricular conduction.[55] Dobutamine can also cause idiosyncratic adverse effects including eosinophilia and fever.[68,69] Generally, these adverse effects are rapidly reversible because of its short plasma half-life, indicating that >98% of the drug is eliminated within 10–12 min after cessation of the infusion.[67] Tolerance can develop after just a few days of therapy.[70]

The effectiveness and safety of dobutamine has mainly been compared with that of milrinone, a drug with similar pharmacodynamic characteristics. A meta-analysis including patients with low CO states and/or CS showed a non-significant trend towards a reduction in mortality with milrinone compared to dobutamine.[71] However, the recent DOREMI (Dobutamine Compared with Milrinone) randomized controlled trial comparing dobutamine versus milrinone in CS showed neutral results.[38] A subsequent meta-analysis reported a significant overall benefit of milrinone over dobutamine in patients with acute HF with or without CS, but mostly included observational studies and cannot be used to draw definitive conclusions in the CS setting.[72]

Phosphodiesterase-III inhibitors

Milrinone is a non-catecholamine inotropic agent, introduced in the early 1990s for the treatment of advanced HF and CS.[73] As previously mentioned, milrinone acts by inhibiting PDE-III, resulting in a reduction in cAMP degradation, thus mimicking the activation of the β_1- and β_2-receptors.[74] As a final result, milrinone leads to an increase in CO through increased inotropy and a reduction in SVR and pulmonary vascular resistance. Milrinone also has lusitropic properties that are manifested by improving diastolic function.[48] It increases the HR, but not to the same extent as dobutamine.[48] The dosage ranges from 0.0625 to 0.5 μg/kg/min.[73] It has a relatively long plasma elimination half-life.[48] For this reason, if hypotension or arrhythmia occurs, these adverse effects may persist for hours.[75] Since milrinone is renally cleared,[48] it should be used with caution in patients with severe renal impairment, with careful management of the dosage used. Currently there is no evidence of clear harm with this drug on renal function, but, on the contrary, milrinone may improve renal function.[76] Similar to milrinone, enoximone is a non-glycoside, non-catecholamine, imidazolone derivative that selectively inhibits PDE-III, leading to increased levels of intracellular cAMP.[27]

Importantly, due to their pharmacodynamic characteristics, compared with drugs acting on the β-adrenergic receptors, and similarly to levosimendan, PDE-III inhibitors maintain their favourable haemodynamic effects in patients on ongoing β-blocker treatment.[77]

In a retrospective analysis of initial inotrope therapy in patients with CS (mostly post-cardiac surgery), Lewis *et al.*[78] found no difference between milrinone and dobutamine in the time to CS resolution. Dobutamine was limited by the development of arrhythmias while milrinone was associated with more hypotension. Similarly, as previously mentioned, in the recent head-to-head comparison between dobutamine and milrinone among patients with CS performed in the randomized DOREMI trial, no drug seems to prevail over the other with no significant differences with respect to primary or key secondary outcomes.[38] Although meta-analyses seem to show a superiority of milrinone versus dobutamine, they mostly included non-randomized studies and significant bias cannot be excluded.[71,72] Milrinone may be considered as an alternative initial inotrope for patients in CS, particularly in patients receiving β-blockers, as it does not use the β-adrenergic receptor to guide cardiac contractility.[79,80] However, it is important to note that β-blocker therapy did not attenuate the effect of dobutamine in the DOREMI trial.[81]

Enoximone can also be used in CS,[82–84] even in addition to adrenergic agents, showing an increase in cardiac index without significant change in MAP. However, data in this setting have been extrapolated from small studies. In addition, the superiority of levosimendan significantly reduced the use of enoximone in CS.[39]

Importantly, PDE-III inhibitors should not be combined because of their synergistic vasodilatory effects, and the combination with levosimendan should be avoided for the same reasons.

Levosimendan

Levosimendan is a calcium sensitizer[85] that can increase cardiac inotropy through a direct effect on cardiac troponin C. Therefore, it has the advantage of not increasing cAMP or Ca^{2+} itself, both of which are the basis of the negative results with catecholamine use, and its function is not impaired by pre-treatment with β-blockers.[22,86] In addition to its main action, levosimendan averages the opening of ATP-dependent K^+ channels in vascular smooth muscle cells by inducing an increase in blood perfusion and systemic vasodilatation.[86] Similarly, it opens ATP-dependent K^+ channels on the mitochondrial inner membrane resulting in cardioprotection, reduction of infarct size, and mitigation of ischaemia/reperfusion lesions.[86] Finally, levosimendan provides

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selective and potent PDE-III inhibition.[1] Inhibition of PDE-III only, and not PDE-IV, would be insufficient to increase intracellular levels of cAMP to the same levels as by simultaneous inhibition of the two isozymes.[87] This may provide an explanation for the different pharmacological behaviour of levosimendan compared to other PDE-III inhibitors, such as oxygen consumption to increase inotropism.[88] The clinical activity of levosimendan during long-term treatment is mainly governed by its active metabolite OR-1896, which has a much longer half-life (81 vs. 1 h).[89]

The most studied use of levosimendan is in patients with advanced HF.[22,24,40,90–96] Regarding its use in ischaemic patients, after the positive results of the RUSSLAN (Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure After an Acute Myocardial Infarction) study[97] and of the LEAF (LEvosimendan in Acute heart Failure following myocardial infarction) study,[42] including nine patients with AMI-CS, a meta-analysis of placebo-controlled trials of levosimendan in AMI supported the idea that it might have a role in patients with AMI-CS.[98] In fact, levosimendan, over an inotropic effect, has a positive effect on ventriculo–arterial coupling, peripheral vasodilatation consequently increasing tissue perfusion, anti-stunning effects and anti-inflammatory effects.[98] Furthermore, its protective effects on the myocyte may have an impact on long-term mortality after AMI.[99,100]

Experience with levosimendan in CS is limited. Levosimendan appears to be well tolerated in addition to the afore-mentioned haemodynamic effects.[39,41,43,101–103] In a small randomized trial, 22 consecutive AMI-CS patients were randomly assigned to levosimendan or dobutamine. A significant increase in cardiac power output at 24 h was more frequent with levosimendan than with dobutamine, while the decrease in pulmonary capillary wedge pressure (PCWP) was similar.[43] No further change in systolic BP was noted in either group, nor serious side effects requiring early withdrawal of the study drug infusion were reported. Furthermore, in another prospective, randomized, controlled, single-centre clinical trial, levosimendan infusion was associated with higher 30-day survival as compared to enoximone (69% vs. 37%, $p = 0.023$) in patients with severe refractory AMI-CS on top of current therapy (including revascularization, intra-aortic balloon pump [IABP], and inotropes).[39] In addition, in this study, levosimendan induced a trend towards higher cardiac index, cardiac power index, LV stroke work index, and mixed venous oxygen saturation. However, data on the impact of levosimendan on survival in CS are not conclusive.[41,103,104] In a recent Cochrane meta-analysis including 19 randomized trials enrolling patients with CS or low CO syndrome, no clear benefit of levosimendan versus dobutamine, enoximone or placebo was observed.[105] Important, the overall quality of evidence was limited with a high risk of bias and imprecision. Thus, no conclusions on the superiority of any therapy over the other could be drawn.[105]

Other agents

Istaroxime

Istaroxime is a derivative of androstenedione that exerts its effects through a double mechanism of action: (i) inotropic action by inhibiting the activity of Na^+/K^+-ATPase resulting in increased intracellular Ca^{2+} and contractility of cardiomyocyte, in a similar way to digitalis; and (ii) lusitropic action through the activation of the SERCA2a in order to promote the reuptake of Ca^{2+} and improving relaxation as well as potentially reducing the risk of arrhythmias.[32] In dogs with advanced HF, istaroxime elicits potent positive luso-inotropic effects.[106] Unlike classic cAMP-dependent positive inotropic agents, istaroxime elicits its benefits without increasing myocardial oxygen consumption or HR.[106] These positive results have been confirmed in the HORIZON-HF (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure) study enrolling patients with acute HF.[32] The main side effects were vomiting and pain at the infusion site.

The SEISMiC study[44] was designed to compare the safety and efficacy of istaroxime versus placebo in patients hospitalized for acute HF-related pre-CS (SCAI stage B), i.e. persistent hypotension without clinical signs of hypoperfusion. Sixty patients were randomized to istaroxime 1.0–1.5 μg/kg/min or placebo for 24 h. Istaroxime increased systolic BP both at 6 h ($p = 0.017$) and 24 h ($p = 0.025$) and improved some echocardiographic parameters at 24 h such as cardiac index (+0.21 L/min/m^2, $p = 0.016$), left atrial area (−1.8 cm^2, $p = 0.008$) and LV end-systolic volume (−12.0 ml, $p = 0.034$). There were no significant differences in pulse pressure, laboratory measurements and serious adverse events between the treatment groups except for more nausea, vomiting and infusion site pain among istaroxime-treated patients. In a post-hoc analysis, patients receiving ≤1.0 μg/kg/min versus 1.5 μg/kg/min had similar increase in BP, but a trend towards less adverse events.[107]

Angiotensin II

Angiotensin II is an octapeptide, component of the renin–angiotensin–aldosterone system, which has multiple physiological actions.[108] It acts on specific receptors, namely angiotensin receptor type 1 (AT_1) and type 2 (AT_2). The major physiologic effects in humans are mediated by the AT_1 receptor, including direct vasoconstriction (via receptors located in the endothelium of peripheral vessels), inotropy and cardiac remodelling (via receptors located in the myocardium), potentiation of the sympathetic nervous system, vasopressin release, regulation of the thirst mechanism (via receptors in the brain, sympathetic ganglia, and pituitary gland), and regulation of aldosterone release (via receptors in the adrenal gland).[109] The observation that angiotensin II causes an increase in slow inward Ca^{2+} current in association with a positive inotropic effect in cardiac Purkinje fibres has been used to indirectly support that its effects on contractility are predominantly mediated by an increase in free intracellular Ca^{2+}.[110] However, Ikenouchi *et al.*[108] demonstrated that angiotensin II positive inotropic effects are predominantly mediated by an increase in myofilament Ca^{2+} sensitivity due to intracellular alkalosis rather than an increase in free cytosolic Ca^{2+}. Because of its rapid degradation, its half-life is ∼30 s in the circulation; however, in the tissues, the half-life is extended to 15–30 min.[109] After the early positive results of the ATHOS (Angiotensin II for the Treatment of

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High Output Shock) trial,[111] the use of human-derived synthetic angiotensin II was approved after the ATHOS-3 trial.[112] This trial excluded CS, but demonstrated that the use of angiotensin II in refractory vasodilatory shock resulted in significant improvements in MAP with decreased use of other vasopressors.[113] Similarly, in a multicentre observational cohort study[114] of angiotensin II use in shock, angiotensin II demonstrated a vasopressor effect within 30 min and reduced catecholamine dose. Recently, a systematic review showed encouraging data on the use of angiotensin II also in CS. In fact, Bansal *et al.*[115] showed that angiotensin II was associated with improvements in MAP, decrease in vasopressor requirements, and minimal reported adverse events. Another potentially interesting application of angiotensin II may be to reverse the effect of renin–angiotensin–aldosterone system inhibitors in CS patients, mainly acute decompensated HF (ADHF)-related CS, who are treated with these medications before admission.[116]

A systematic review evaluating the safety of angiotensin II among 31 281 subjects across 1124 studies in any clinical setting found that adverse events were infrequent and that angiotensin II had an acceptable safety profile.[117] Common side effects included headache, sensation of chest pressure, dyspepsia, orthostatic hypotension upon cessation of the drug, and worsening bronchoconstriction during an asthma exacerbation.[109] However, due to the lack of robust evidence-based data on angiotensin II in CS, it is currently not recommended in this setting and further dedicated studies are needed to explore its safety and efficacy profile.

Vasopressin

The nonapeptide vasopressin is mainly released by the pituitary gland after increased plasma osmolality or hypotension, but it can also be synthesized by the heart in response to elevated wall stress.[47] Vasopressin stimulates the V1 receptors of vascular smooth muscle and is a powerful vasoconstrictor, especially at the systemic level, while at the level of the pulmonary circulation the density of receptors is lower, without chronotropic nor inotropic properties.[53] In addition, efferent renal arterioles have a higher density of vasopressin receptors than afferent renal arterioles, which could increase the glomerular filtration pressure.[53] Finally, vasopressin causes an increase in vascular sensitivity to norepinephrine increasing its pressor effects and reduces nitric oxide (NO) production, an important mediator of vasoplegia during systemic inflammatory response syndrome.[118] The action is effective even during hypoxic and acidotic conditions, typical of patients in shock.[55] Vasopressin has been extensively studied in septic shock, showing among the side effects a risk of myocardial or splanchnic ischaemia with increased dose.[119–121] In contrast, there is little evidence for the use of vasopressin in CS. In a retrospective study of 36 patients with AMI-CS despite inotropic/vasopressor therapy, intravenous vasopressin therapy increased MAP from 56 to 73 mmHg at 1 h ($p < 0.001$) and maintained it for 24 h without changing PCWP, cardiac index, urine output, or other inotropic requirements.[122] Vasopressin in CS may be an alternative in tachycardic patients, in those with pulmonary hypertension,[53] and in dynamic LV outflow obstruction where a vasopressor with inotropic properties like norepinephrine could be detrimental as increasing cardiac contractility would worsen the LV outflow obstruction and further compromise forward flow.[73] However, in the absence of solid data on its use in CS, it is currently not recommended in this setting and further studies are needed to explore its usefulness.

Procizumab

Circulating dipeptidyl peptidase 3 (cDPP3) is a protease involved in the degradation of angiotensin II and enkephalins, known since 1967. Recently, it has been discovered that it is implicated in pathophysiologic processes such as inflammation, BP regulation, and pain modulation. In addition, animal studies have shown that cDPP3 significantly affects cardiac contractility with a negative inotropic effect.[123] In particular, high cDPP3 values have been found in severely ill patients with CS. In the OptimaCC study, cDPP3 values were higher in refractory CS than non-refractory CS at inclusion ($p = 0.014$), at 24 h ($p < 0.001$) and up to 48 h ($p = 0.027$). More importantly, among CS patients with high cDPP3 at inclusion, those who quickly decreased cDPP3 at 24 h showed a noticeable reduction in the occurrence of refractory shock and death.[124] Procizumab, a specific antibody directed against cDPP3, was tested in a model of acute HF mouse where it promptly normalized cardiac function and renal haemodynamics with a concomitant reduction in oxidative stress and inflammation.[125] The potential role of this antibody in CS remains to be assessed.

Nitric oxide synthase inhibitors

Excessive NO synthase activity results in high levels of NO that lead to inappropriate systemic vasodilatation, progressive systemic and coronary hypoperfusion, and myocardial depression.[46] NO synthase inhibitors have proven to be effective in patients with refractory AMI-CS.[45,126,127] However, in the TRIUMPH (Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock) trial, tilarginine did not reduce the duration of shock, 30-day and 6-month mortality in 398 patients with refractory AMI-CS despite revascularization.[46]

Methylene blue (MB) is a phenothiazine-related heterocyclic aromatic molecule, potent inhibitor of NO synthase in vascular endothelial cells resulting in decreased NO release and increased SVR.[128] MB has demonstrated beneficial effects on severe vasodilatation associated with distributive shock and vasoplegia after cardiopulmonary bypass.[128,129] Beyond NO synthase inhibition, its positive effects in refractory shock may also be due to an improvement in mitochondrial respiration.[130–132] In a recent retrospective cohort study including 262 patients with shock despite norepinephrine dose >0.1 µg/kg/min, CS increased the chance of responding to MB (adjusted OR 2.21, 95% CI 1.11–4.36).[133] MB could therefore be considered in patients with CS and concomitant distributive shock who do not respond to standard treatment. The dosing regimen for MB seems to be 1–2 mg/kg. The use of high doses of MB, typically greater than 7 mg/kg, is associated with adverse effects such as paradoxical induction of methemoglobinaemia, acute haemolytic anaemia, and detrimental effects on pulmonary function.[129]

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Inotropic therapy in different clinical scenarios

Acute left ventricular failure

To date, there are no convincing data supporting any specific therapy to reduce mortality in patients with CS.[105] The selection of the vasopressor and/or inotropic agent should take into account the patient's haemodynamic profile and primarily the severity of hypotension.[134]

When BP needs to be quickly restored to improve perfusion to vital organs by maintaining an adequate MAP, vasopressors, particularly norepinephrine, represents the first-line agent.[34,36] Various studies showed that norepinephrine is safer than dopamine,[34] vasopressin,[122] or epinephrine,[36] with a lower risk of atrial arrhythmias.[59] However, considering that reduced CO may be the primary cause of CS, the use of an inotropic agent as upfront strategy may be considered as logical. In case of use of inotropic agents with vasodilatory properties, such as PDE-III inhibitors or levosimendan, concomitant administration of norepinephrine may be advised to prevent or avoid hypotension.

The presence of chronic β-blocker therapy might influence the choice of the inotropic agent. In a sub-analysis of the DOREMI trial, β-blocker therapy in the 24 h preceding the development of CS did not negatively influence the primary composite outcome (risk ratio [RR] 0.96, 95% CI 0.73–1.27, $p = 0.78$) or haemodynamic parameters. On the contrary, β-blocker use was associated with fewer early deaths (RR 0.41, 95% CI 0.18–0.95, $p = 0.03$), suggesting a protective effect also in patients with CS.[81] These data are in agreement with previous studies showing that the administration of dobutamine, but not of enoximone, in patients on concomitant β-blocker therapy causes an increase in peripheral and pulmonary vascular resistance with a blunted CO response.[77] Consistently, an analysis of the SURVIVE (Survival of Patients with Acute Heart Failure in Needs of Intravenous Inotropic Support) trial showed a beneficial effect of levosimendan, but not of dobutamine, in patients treated with β-blockers.[135]

The choice of inotropes/vasopressors may also be affected by the aetiology of CS (*Figure 2*).[136] AMI-CS was associated with significantly lower SVR and a trend towards higher cardiac index compared to ADHF-CS.[137] Such low SVR may be related to systemic inflammation in relation to myocardial necrosis triggered by interleukins, tumour necrosis factor-α and inducible NO synthase. On the other hand, in patients with ADHF-CS, the profound upregulation of vasoconstrictor substances such as angiotensin II, endothelin-1 and norepinephrine may explain the relatively preserved compensatory vasoconstriction.[137] Specific cardiovascular responses are further modified by reflexive autonomic changes after acute BP alterations, which impact HR, SVR, and other haemodynamic parameters. Adrenergic receptors can be desensitized and down-regulated in certain conditions, such as in chronic HF, or in long-standing CS. Binding affinities of individual inotropes and vasopressors to adrenergic receptors can also be altered by hypoxia or acidosis, which mutes their clinical effect.[138]

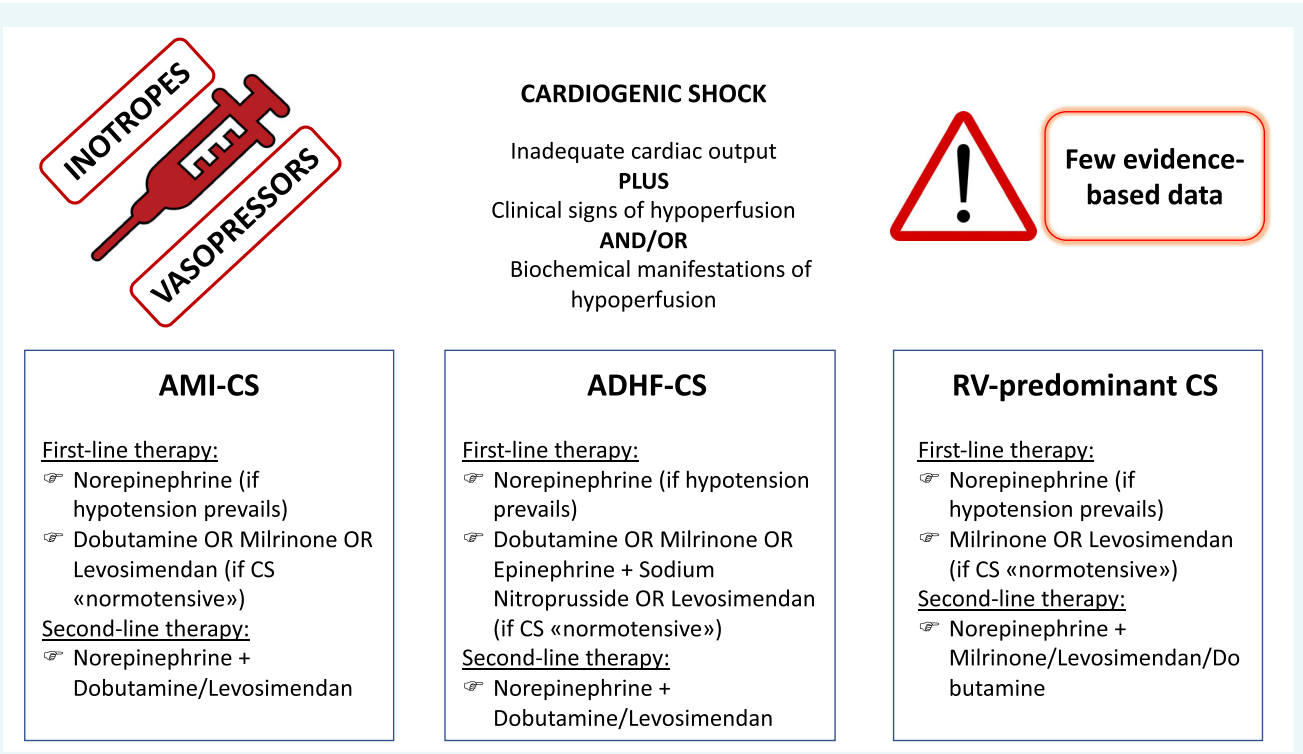

Figure 2 Current options for inotropic/vasopressor therapy in cardiogenic shock (CS). Despite the presence of few evidence-based data, a therapeutic algorithm is proposed based on patient's haemodynamic profile and aetiology of CS. ADHF-CS, acute decompensated heart failure-cardiogenic shock; AMI-CS, acute myocardial infarction-cardiogenic shock; RV, right ventricular.

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Finally, systemic vasoconstriction preserves perfusion in organs with autoregulation (i.e. heart and brain) but it worsens perfusion in organs without autoregulation (i.e. splanchnic organs including liver, skin, partially kidney), and prolonged vasoconstriction increases inhomogeneity of perfusion in any organ.

It may be reasonable to think that patients with AMI-CS can benefit from a vasopressor as first-line therapy while patients with ADHF-CS may benefit from an inodilator, particularly in the absence of profound hypotension with concomitant administration of an inodilator and a vasopressor (norepinephrine) in the latter case.[2] However, due to the lack of robust evidence on a tailored medical treatment in AMI-CS versus ADHF-CS, further studies are needed to explore differential inotrope/vasopressor combinations in these CS subtypes before drawing definitive conclusions. In the absence of evidence from clinical trials, potentially interesting information can be derived from observational data (*Table 3*).[11,59,139–141]

During vasopressor treatment in CS, three stages may be identified (*Figure 3*): (1) *mechanical efficiency* with increase in SVR and MAP; (2) *mechanical inefficiency* with worsening microcirculatory dysfunction and a disconnection between macro- and microcirculation, with further vasodilatation and a trend towards a reduction in MAP and worsening organ injury; and (3) *metabolic inefficiency* due to a combined effect of desensitization of adrenoreceptors exposed to high doses of catecholamines for prolonged time, vasoplegia, acidosis, systemic inflammatory response syndrome with or without infection, and progressive end-organ damage up to multi-organ failure. In this latest stage with marked vasoplegia, switching from norepinephrine to vasopressin may be logical (*Figure 3*).

Concomitant administration of pure HR-lowering agents, such as ivabradine, or short-acting β-blockers, such as landiolol, may be useful to counteract catecholamine-induced tachycardia.[142–144] A randomized, double-blind, single-centre trial (NCT03387605) is ongoing to study of the effects of ivabradine versus placebo in patients hospitalized for stage D HF and CS who require continuous infusion of dobutamine and develop sinus tachycardia.

Acute right ventricular failure

Acute right ventricular (RV) failure can be defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output. It may be associated with increased RV afterload or preload and consequent RV chamber dilatation and tricuspid regurgitation.[145] Left-sided HF, acute pulmonary embolism and AMI are the most common causes.[146] Acute RV failure may complicate LV-dominant CS, thus resulting in biventricular CS, or cause RV-dominant CS *per se*.[147,148] The identification of concomitant or predominant RV impairment in CS has relevant prognostic and therapeutic implications.[149]

Patients with RV failure may be preload-dependent, but, at the same time, the volume load has the potential to distend the right ventricle, in turn, compromising LV filling, and thus systemic CO.[150] For this reason, in these patients, careful volume assessment and management is necessary by combining an appropriate volume load guided by central venous pressure monitoring (with target value <12 cmH_2O) and a judicious use of diuretics.[145,146,151,152] Of note, when considering RV afterload, hypoxia and acidosis worsen pulmonary hypertension causing pulmonary vasoconstriction, thus increasing RV afterload. These two conditions must therefore be identified and, if present, properly treated.[153] In addition, mechanical ventilation should always be used cautiously in RV failure. Lowest tidal volume and positive end-expiratory pressure providing adequate oxygenation is recommended.[154]

Vasopressors and/or inotropes are indicated also in this setting in case of haemodynamic instability and/or signs of hypoperfusion.[146] Norepinephrine remains the drug of choice when the goal is to restore BP and improve perfusion.[151,153] Animal studies suggest that norepinephrine increases CO and decreases biventricular filling pressures in RV failure without significantly increasing RV afterload,[155] especially if used at lower doses. In patients with persisting hypoperfusion despite optimization of preload and afterload and use of norepinephrine, dobutamine may be considered.[27] The use of epinephrine and dopamine is discouraged based on the results of OptimaCC[36] and SOAP-II,[34] respectively. Levosimendan and PDE-III inhibitors can favourably influence RV–arterial coupling by combining inotropy and pulmonary vasodilatation, without the deleterious effects on pulmonary vascular resistance that can occur with catecholamines.[146] As a result, levosimendan and PDE-III inhibitors may be indicated preferentially over dobutamine, especially in patients with pulmonary hypertension caused by left heart disease.[146] Mechanistic studies showed pulmonary vasoconstriction, likely due to α-adrenergic stimulation not counteracted by β_2-adrenergic agonism, when dobutamine is administered to patients on β-blockers.[77] However, a subgroup analysis of the DOREMI trial did not show a benefit of milrinone over dobutamine in patients with isolated RV failure, although the trial was underpowered to answer this question.[38] In addition, like dobutamine, these drugs can aggravate arterial hypotension and should be combined with norepinephrine if necessary. Lastly, it is important to highlight that bradycardia is particularly detrimental in RV failure and, if persistent, pacing is indicated. In this setting, dobutamine or epinephrine can at least theoretically counterbalance bradycardia rather than PDE-III inhibitors.

Escalation and de-escalation: The importance of a multistep tailored strategy

The ideal treatment of CS should be a multistep process customized to the haemodynamic and metabolic characteristics of the patient (*Figure 4*).[156] In addition to recognizing and treating the cause responsible for CS, the first aim is to maintain adequate tissue perfusion ('rescue phase').[156] As mentioned above, at this stage vasopressor drugs, particularly norepinephrine, are the first choice.[2] Pulmonary artery catheter (PAC) placement can be useful to guide therapy selection and use. Continuous PAC assessments combined with non-invasive imaging may also facilitate the appropriate escalation of therapy if clinical improvement is not achieved with the initial therapeutic strategy.[157,158] The use of PAC has recently been associated with improved survival in patients with CS and its increased use may be warranted until evidence will come from proper prospective randomized trials.[159–161]

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Table 3 Real-word data on the use of inotrope/vasopressor therapy in cardiogenic shock

Study, year	No. of patients	CS aetiology	Strategy	First-line vasopressor	First-line inotrope	Notes
ESC-ACVC Network, 2022[139]	309	Ischaemic (79.9%) ADHF (13.4%) Myocarditis (3.5%) Right HF (0.35%) Other (2.85%)	Inotropes (35.9%) Vasopressors (26.4%) Vasopressor–inotrope combination (37.7%)	Norepinephrine (89.9%) Dopamine (8.5%) Other (1.6%)	Dobutamine (65.5%) Dopamine (10.5%) Epinephrine (9.3%) PDE3-I (6.2%)	Adrenergic drugs demonstrated severe metabolic and haemodynamic adverse effects. Dopamine is still used in Level I hospital, both as vasopressor and inotrope.
CardShock study, 2016[59]	219	Ischaemic (81%)	Vasopressor–inotrope combination (60%) Inotropes (10%) Vasopressors (30%)	Norepinephrine (75%) Dopamine (26%) Vasopressin/terlipressin (4%) Epinephrine (21%)	Dobutamine (49%) Levosimendan (24%) PDE3-I (4%)	Norepinephrine with dobutamine or levosimendan were the most widely used combinations and were associated with a more positive outcome. Epinephrine, regardless of the maximum infusion rate, was consistently associated with worse outcome. Dopamine was often used at renal inotropic dose.
FRENSHOCK Registry, 2022[140]	772	Ischaemic (36.3%) Supraventricular arrhythmias (13.3%) Ventricular arrhythmias (12.6%) Infectious disease (11.9%)	Vasopressor–inotrope combination (45.6%)	Norepinephrine (53.1%) Dopamine (0.3%)	Dobutamine (81.9%) Epinephrine (12.4%) Levosimendan (7.4%) Milrinone (1.8%) Enoximone (0.4%)	Norepinephrine with dobutamine was the most widely used combination. Norepinephrine use was independently associated with 30-day mortality (OR 2.55, 95% CI 1.69–3.84)
RESCUE Registry, 2021[11]	1247	Ischaemic (80.7%) Dilated cardiomyopathy (6.1%) Myocarditis (3.2%) Ventricular arrhythmia (2.5%)	Vasopressors (86.7%)	Dopamine (63.4%) Norepinephrine (57.3%) Epinephrine (6.9%)	Not reported	The amount of vasopressor was a poor prognostic factor for in-hospital mortality.
Retroshock, 2022[141]	1249	Ischaemic (100%)	Not reported	Norepinephrine (84%) Dopamine (65%) Epinephrine (25%)	Inodilators (30%)	Norepinephrine was the preferred vasopressor irrespective of SCAI stage (dosage increased with increasing SCAI stage). Epinephrine and inodilators were most frequent in SCAI stage E. Combinations of vasopressors were more frequent in SCAI stage D and E. There was no significant association between ventricular arrhythmias and vasopressor choice in each SCAI stage. There was no significant difference in mortality regarding the vasoactive regimes in SCAI stage D and E, but in SCAI stage C mortality was higher in patients receiving epinephrine.

ADHF, acute decompensated heart failure; CI, confidence interval; CS, cardiogenic shock; HF, heart failure; OR, odds ratio; PDE3-I, phosphodiesterase-III inhibitor; SCAI, Society for Cardiovascular Angiography and Interventions.

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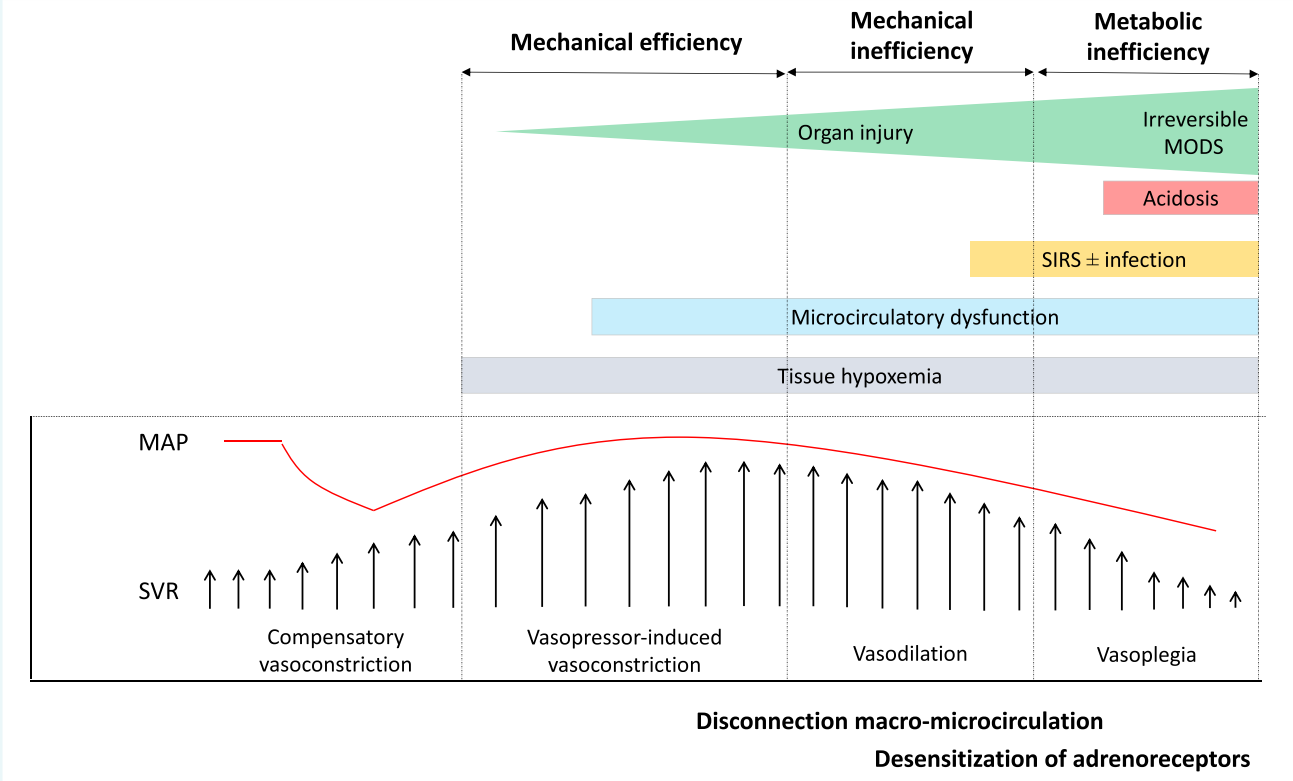

Figure 3 Shock stages during vasopressor treatment. Three stages may be identified during vasopressor treatment: mechanical efficiency (increase in systemic vascular resistance [SVR] and mean arterial pressure [MAP]), mechanical inefficiency (microcirculatory dysfunction, disconnection between macro- and microcirculation, vasodilatation with MAP reduction and worsening organ injury) and metabolic inefficiency (desensitization of adrenoreceptors, vasoplegia, acidosis, systemic inflammatory response syndrome [SIRS]with or without infection, progressive end-organ damage up to multi-organ dysfunction syndrome [MODS]).

After the 'rescue phase', the goal is to tailor the pharmacological support to the haemodynamic status until reaching a phase of stability ('optimization phase').[156] A MAP >65 mmHg may be considered a reasonable target for treatment.[157,162] However, minimal acceptable MAP has inter-individual variability with patients with ADHF who may tolerate lower MAP. The balance between the risk of impaired coronary and systemic perfusion in case of low MAP and of increased myocardial oxygen demand, increased afterload and arrhythmias with higher MAP should be found.[163] A recent analysis showed that AMI-CS patients with higher MAP targets (85–100 mmHg) had less biochemical evidence of myocardial injury than patients with a MAP target of 65 mmHg.[164] Similarly, in a post-hoc analysis of CAPITAL-DOREMI, low MAP (<70 mmHg) was associated with worse clinical outcome.[163] On the contrary, Gaubert *et al.*[137] demonstrated that patients with ADHF-CS present with low cardiac index and high SVR. In fact, ADHF is mechanistically characterized by a ventricular afterload mismatch without preload reserve: as a result, CO is exquisitely sensitive to changes in afterload and may improve simply with afterload reduction.[165] Hence, it can be assumed that in such patients a lower target MAP (i.e. 55–60 mmHg) can be reasonable.

Beyond optimization of medical treatment, the use of short-term MCS should also be considered to further support cardiac function and increase organ perfusion.[21,66] Of note, the use of MCS may allow de-escalation and potentially complete weaning from inotropes and vasopressors, thus reducing the drug-related adverse effects in terms of myocardial damage and/or stabilize haemodynamic conditions when the patients does not respond to medications.[166] Persistence of elevated LV filling pressures, pulmonary congestion, metabolic decompensation, ongoing hypoperfusion and end-organ damage during first-line MCS are criteria for escalation to second-line MCS.[21,74] In this setting, it is also important to select a strategy in relation to long-term perspectives (bridge-to-recovery or bridge-to-heart replacement therapies, i.e. LV assist device or heart transplantation).[21,74]

Once haemodynamic stabilization has been reached and maintained, with adequate tissue perfusion and reversal of end-organ damage, the goal is to start de-escalation and the 'weaning phase', in order to keep devices and drugs as short as possible. Progressive de-escalation always needs to be guided by the patient's haemodynamic profile (including MAP, markers of tissue perfusion, imaging and invasive data). The optimal timing to initiate weaning has not been well studied,[167] but it is reasonable to begin it on resolution of cardiac dysfunction or evidence of at least partial myocardial recovery, improvement in end-organ hypoperfusion, intravascular euvolaemia, and improved ventricular contractility on

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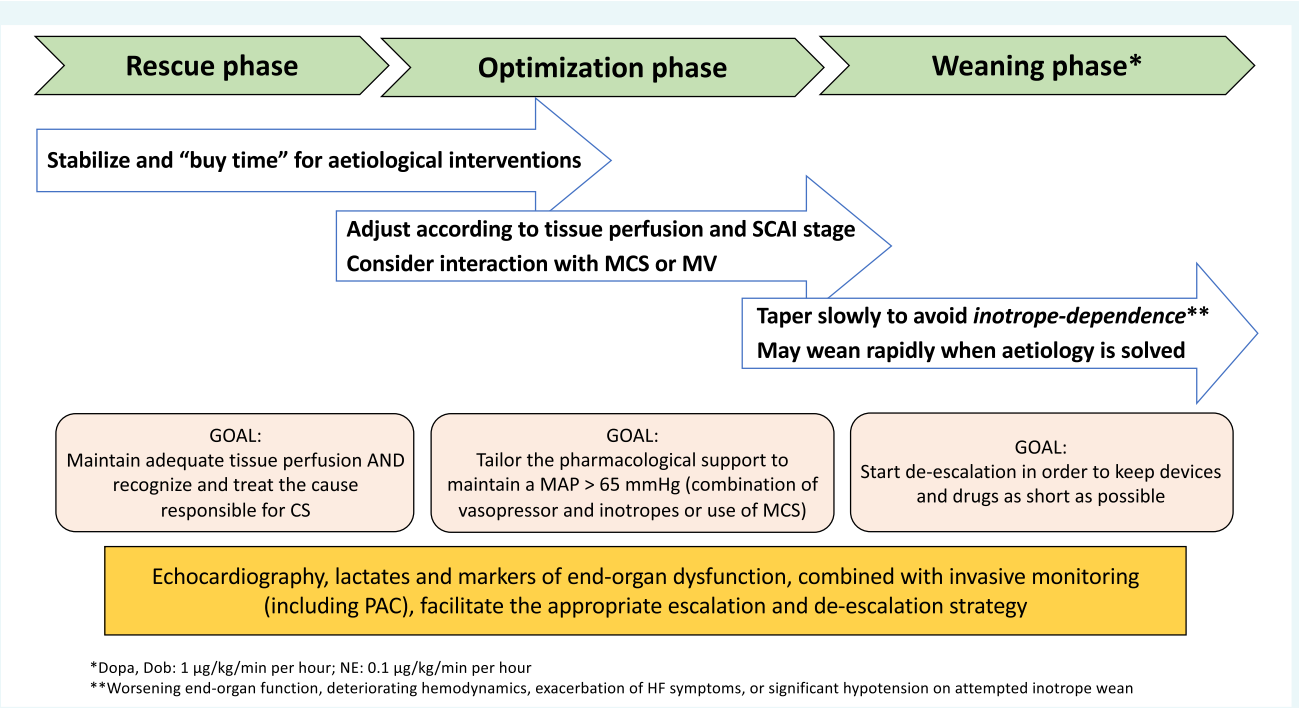
Rescue phase
Optimization phase
Weaning phase*
Stabilize and "buy time" for aetiological interventions
Adjust according to tissue perfusion and SCAI stage
Consider interaction with MCS or MV
Taper slowly to avoid inotrope-dependence**
May wean rapidly when aetiology is solved
GOAL:
Maintain adequate tissue perfusion AND recognize and treat the cause responsible for CS
GOAL:
Tailor the pharmacological support to maintain a MAP > 65 mmHg (combination of vasopressor and inotropes or use of MCS)
GOAL:
Start de-escalation in order to keep devices and drugs as short as possible
Echocardiography, lactates and markers of end-organ dysfunction, combined with invasive monitoring (including PAC), facilitate the appropriate escalation and de-escalation strategy
*Dopa, Dob: 1 μg/kg/min per hour; NE: 0.1 μg/kg/min per hour
**Worsening end-organ function, deteriorating hemodynamics, exacerbation of HF symptoms, or significant hypotension on attempted inotrope wean

Figure 4 Multi-step tailored strategy in cardiogenic shock (CS). A multi-step approach is useful in the management of patients with CS. The immediate goal is to maintain adequate tissue perfusion, using vasopressors, inotropes and mechanical circulatory support (MCS), also in combination when appropriate. In the meantime, it is important to start recognizing and treating the cause of CS. Once the patient has been stabilized, tissue perfusion is adequate, end-organ function is recovered or stabilized, and cardiac function is 'sufficient', the goal is to keep the vasopressors/inotropes as short as possible to avoid the risk of long-term mortality associated with these drugs. Dob, dobutamine; Dopa, dopamine; HF, heart failure; MAP, mean arterial pressure; MV, mechanical ventilation; NE, norepinephrine; PAC, pulmonary artery catheter.

echocardiography.[157] These concepts may be applied to weaning from both MCS and drugs. Rapid weaning may be more appropriate for patients with AMI-CS who were fully revascularized and had a recovery in ejection fraction or for patients with CS attributable to a valvular lesion that has subsequently resolved. Alternatively, a slower weaning may be appropriate for patients with ADHF-CS which can often be initiated when the patient is euvolaemic or near euvolaemic.[157] Due to its ability to accurately identify the patient's haemodynamic profile and the presence and degree of concomitant RV dysfunction, PAC may have a central role in this setting, although evidence from prospective studies is lacking, yet. A cardiac index $\leq$2.2 L/min/m^2 associated with a PCWP $\geq$15 mmHg has been the traditional haemodynamic criterion for left-sided CS.[168] As mentioned above, in this setting, the use of an inotropic agent as upfront strategy may be considered as logical. PAC can also be useful in the evaluation of SVR: in patients with elevated SVR, the use of an inodilator may be considered,[169] while in patients with low SVR the use of vasopressors is more appropriate. Lastly, a pulmonary artery pulsatility index <0.9 has been described as the strongest indicator of severe RV failure and may be useful to optimize inotropic support and/or identify patients needing RV MCS.[168] The use of PAC may allow better indication for the escalation and de-escalation strategies and, accordingly, it has recently been associated with improved survival in patients with CS.[159–161,168,170]

Concomitant mechanical circulatory support treatment

The use of temporary MCS has significantly increased in recent years, becoming an alternative to inotropic support in patients with CS or an additional strategy in patients who are refractory to inotropic/vasopressor therapy.[171] Few data are available on the use of inotropic therapy during concomitant MCS. The best strategy could be a personalized approach based on the characteristics of the device used.

The IABP increases only modestly CO (0.5 L/min), but significantly reduces LV afterload, decreasing myocardial demand of oxygen, and improves coronary blood flow.[165] The ideal goal should be to de-escalate inotropic therapy during IABP support in CS. However, due to its modest effect on CO, concomitant inotropic/vasopressor therapy remains frequently needed.

The Impella device (Abiomed, Danvers, MA, USA) can rapidly improve MAP and decrease both LV pressure and volume, resulting in LV unloading and reduced myocardial oxygen consumption.[172] Considering the relevant support provided by this device in terms of CO (peak flows up to 4.3 L/min with Impella CP and up to 6 L/min with Impella 5.5), a trial of de-escalation of pharmacological therapy once haemodynamic stability is achieved with MCS can be feasible. Of note, persistent inotropic support is frequently needed in case of concomitant RV dysfunction, although

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Table 4 Main ongoing trials on the medical treatment of cardiogenic shock

Trial	Registration number	Trial design	Arms	Estimated enrolment	Primary endpoint
CAPITAL DOREMI 2	NCT05267886	Randomized	Inotrope (milrinone or dobutamine) vs. placebo	$n = 346$	All-cause mortality during hospitalization or any of these: sustained hypotension or sustained requirement of high-dose vasopressors; lactate >3.5 mmol/L at 6-h; need for MCS; atrial or ventricular arrhythmia; resuscitated cardiac arrest
WEANILEVO	NCT04158674	Randomized	Levosimendan vs. placebo	$n = 210$	ECLS withdrawal failure
LEVOECMO	NCT04728932	Randomized	Levosimendan vs. placebo	$n = 206$	Time to successful ECMO weaning within 30 days
LevoHeartShock	NCT04020263	Randomized	Levosimendan vs. placebo	$n = 610$	All-cause mortality and/or ECLS implantation and/or dialysis
PANDA	ACTRN1262100805875	Randomized	Norepinephrine vs. epinephrine	$n = 890$	All-cause mortality at 28 days
IVA-CS	NCT05594342	Randomized	Ivabradine + dobutamine vs. dobutamine only	$n = 200$	HR reduction, time of weaning from dobutamine infusion, duration of hospital stays
Afterload reduction with sodium nitroprusside of LVFP under VA-ECMO support	ACTRN12623000467639p	Single-arm	Sodium nitroprusside	N/A	Quantify the extent to which the reduction in MAP affects the LVFP during VA-ECMO support

ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; HR, heart rate; LVFP, left ventricular filling pressure; MAP, mean arterial pressure; MCS, mechanical circulatory support; N/A, not available; VA, venoarterial.

severe RV failure remains an indication to evaluate mechanical RV support.

Unlike IABP and Impella, venoarterial extracorporeal membrane oxygenation (VA-ECMO) can provide both circulatory and respiratory support, generating a circulatory support up to 6 L/min.[173] However, retrograde flow increases LV afterload and diastolic LV pressure, therefore worsening mitral regurgitation and increasing PCWP with the risk of acute pulmonary oedema.[174] Several strategies are available to overcome this drawback following the use of VA-ECMO, including mechanical unloading.[175–178] Although concomitant inotropic therapy may help LV unloading, patients with VA-ECMO and continuous epinephrine infusion had a significantly worse prognosis compared to patients with inodilators or without any inotropic therapy.[179] These data have recently been confirmed in 262 patients receiving epinephrine alone or associated with another catecholamine while on VA-ECMO, showing that epinephrine use was independently associated with mortality.[180] Similarly, Wengenmeyer *et al.*[181] have shown that, during VA-ECMO therapy, mortality increases with increasing vasopressor requirements. Although an inotrope with vasodilatory action, such as levosimendan, can be useful with concomitant VA-ECMO, LV unloading in this setting frequently requires IABP or active MCS.[176,182]

Inotropic therapy is usually needed during weaning from MCS. Unless complete and sustained LV recovery has been achieved before MCS weaning, concomitant inotropic support is frequently used during or after MCS de-escalation. The intensity and combination of drugs need to be adapted to the patient's haemodynamic status, LV function and end-organ function. Vasopressors should be discontinued first, keeping MCS at lowest possible output and then tapering inotropes.

In this setting, there is preliminary evidence on the usefulness of levosimendan during weaning from VA-ECMO.[183–185] In a meta-analysis,[186] levosimendan was associated with a higher likelihood of successful weaning from VA-ECMO and with lower mortality as compared to the controls. These results have been confirmed in another meta-analysis.[187] WEANILEVO (NCT04158674) is an ongoing randomized trial evaluating whether levosimendan (0.2 µg/kg/min for 24 h) is effective in favouring VA-ECMO weaning, as compared to placebo.[188] *Table 4* summarizes the main ongoing trials on the medical treatment of CS. As for other drugs with inodilatory properties, milrinone may be useful for VA-ECMO weaning, although retrospective data suggested worse outcomes with this drug as compared to levosimendan in this setting.[185]

Weaning-induced pulmonary oedema

Weaning-induced pulmonary oedema (WiPO) is a cause of weaning failure related to the transition from a positive pressure to a

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negative pressure regimen of ventilation. This creates unfavourable loading conditions for the heart because of increased RV and LV preload and afterload. This condition can also potentially induce myocardial ischaemia.[189] PAC can detect weaning-induced cardiac failure through a significant increase in PCWP. Since increased cardiac preload is one of the main mechanisms leading to WiPO, the use of appropriate diuretic therapy is essential, keeping in mind that excessive fluid depletion may be deleterious because it may thicken bronchial secretions and generate atelectasis.[190] For this reason, a fluid management strategy driven by natriuretic peptides can be useful in these cases.[191] Inotropes do not seem a logic therapeutic option because the reduction of cardiac contractility is not the main cause and they can increase myocardial oxygen consumption.[190] However, levosimendan has shown benefits in this setting when compared to dobutamine both because of its systemic and pulmonary vasodilatory properties and due to lower oxygen demand.[192] Obviously, failed extubation and subsequent reintubation are independently associated with mortality and morbidity of patients under mechanical ventilation.[193] For this reason, before starting weaning, it is reasonable to wait until the patient has reached a sufficient degree of autonomy, including the absence of vasopressor. Weaning during active support with vasoactive drugs can still be performed, provided that the dosages are low.[194,195]

Conclusions

Cardiogenic shock is a complex multifactorial clinical syndrome with extremely high mortality, which develops as a continuum, resulting from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. Considerable development has not proved effective and safe for most of the therapies tested, and the results in this condition remain poor. Although several pharmacological strategies are available for the medical treatment of CS, their efficacy is still suboptimal, and their associated adverse or deleterious effects are significant. Further dedicated, well-designed, prospective trials are needed to refine the pharmacological strategies and to test novel drugs in the CS setting. In addition, high-quality translational research may facilitate the incorporation of more targeted interventions into clinical research protocols, with the final aim to improve CS prognosis.

Conflict of interest: M.P. has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. O.C. has received grants from Servier. A.M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics, Bayer, and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. G.C. is director of Heart Initiative, a non-profit organization; and is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. F.G. has received consulting fees for Bayer, Alnylam, Ionis, Pfizer, Abbott and speakers fee from AstraZeneca, Novartis and Orion Pharma. M.A. has received speaker fees from Abbott Vascular and Medtronic. M.M. has received personal fees from Actelion, Amgen, Livanova, and Vifor Pharma as a member of executive or data monitoring committees of sponsored clinical trials and from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics for participation in advisory boards or for speaking at sponsored meetings. All other authors have nothing to disclose.

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